



BÖLÜM 24

TİROID VE PARATRÖİD HORMONLARININ KARDİYOVASKÜLER SİSTEM ÜZERİNE ETKİLERİ

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TİROID HORMONLARININ KARDİYOVASKÜLER SİSTEM ÜZERİNE ETKİLERİ

Kardiyovasküler hastalıklar, günümüzde dünya çapında en önde gelen ölüm nedenlerinden birini oluşturmaktadır. Tiroid hormon reseptörlerinin hem miyokardiyal hem de vasküler endotelyal dokularda mevcut olduğu ve böylece tiroid hormon konsantrasyonlarındaki değişikliklerin üç organ aktivitesini modüle etmesine olanak sağladığı göz önüne alındığında, tiroid hormonlarının -özellikle anormal olduğunda- kardiyovasküler hastalığı başlatma ve ağırlaştırmadaki rolü aşikardır.

Moleküler ve Hücresel Mekanizmaları

Tiroid hormonlarının başta kalp olmak üzere kardiyovasküler sistem üzerinde, çok çeşitli etkileri vardır.

Bu etkileri 3 farklı yolla gösterirler:

1. Nükleer reseptörlerle bağlanma yoluyla kardiyomiyositlerde doğrudan genetik etkiler yaparlar; Ana etkilerin birçoğu, nükleer reseptörler aracılığıyla hedef genlerin promotör bölgesinde bulunan tiroide duyarlı elementlere (TRE'ler) bağlanarak etki gösteren T3 tarafından ortaya çıkarılır (1). Bu da hedef genlerin ekspresyonunun düzenlenmesine yol açar; T3, çekirdekteki THR'ler (tiroid hormonu reseptörleri) üzerinde etki ederek 9-cis-retinoik asit

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KAYNAKLAR

1. Jiskra J. Hyperthyroidism and the heart. *Kardiol Rev.* 2018;20(3):167–72.
2. Harvey CB, Williams GR. Mechanism of thyroid hormone action. *Thyroid.* 2002;12(6):441–6.
3. Averyhart-Fullard V, Fraker LD, Murphy AM, Solaro RJ. Differential Regulation of Slow-skeletal and Cardiac Troponin I mRNA during Development and by Thyroid Hormone in Rat Heart. Vol. 26, *Journal of Molecular and Cellular Cardiology.* 1994. p. 609–16.
4. Fazio S, Palmieri EA, Lombardi G, Biondi B. Effects of thyroid hormone on the cardiovascular system. *Recent Prog Horm Res.* 2004;59(Table I):31–50.
5. Kranias EG, Hajjar RJ. Modulation of cardiac contractility by the phopholamban/SERCA2a regulatome. *Circ Res.* 2012;110(12):1646–60.
6. Panagoulis C, Halapas A, Chariatis E, Driva P, Matsakas E. Hyperthyroidism and the heart. *Hell J Cardiol.* 2008;49(3):169–75.
7. Kasturi S, Ismail-Beigi F. Effect of thyroid hormone on the distribution and activity of Na, K-ATPase in ventricular myocardium. *Arch Biochem Biophys.* 2008;475(2):121–7.
8. Chen WJ, Yeh YH, Lin KH, Chang GJ, Kuo CT. Molecular characterization of thyroid hormone-inhibited atrial L-type calcium channel expression: Implication for atrial fibrillation in hyperthyroidism. *Basic Res Cardiol.* 2011;106(2):163–74.
9. Vargas-Uricoechea H, Bonelo-Perdomo A, Sierra-Torres CH. Effects of thyroid hormones on the heart. *Clin e Investigaen Arterioscler [Internet].* 2014;26(6):296–309. Available from: <http://dx.doi.org/10.1016/j.arteri.2014.07.003>
10. Silva JE, Bianco SDC. Thyroid-adrenergic interactions: Physiological and clinical implications. *Thyroid.* 2008;18(2):157–65.
11. Park KW, Dai HB, Ojamaa K, Lowenstein E, Klein I, Sellke FW. The direct vasomotor effect of thyroid hormones on rat muscle resistance arteries. *Anesth Analg.* 1997;85(4):734–8.
12. Vargas F, Rodríguez-Gómez I, Vargas-Tendero P, Jimenez E, Montiel M. The renin-angiotensin system in thyroid disorders and its role in cardiovascular and renal manifestations. *J Endocrinol.* 2012;213(1):25–36.
13. Fadel BM, Ellahham S, Ringel MD, Lindsay J, Wartofsky L, Burman KD. Hyperthyroid heart disease. *Clin Cardiol.* 2000;23(6):402–8.
14. Ertek S, Cicero AF. Hyperthyroidism and cardiovascular complications: A narrative review on the basis of pathophysiology. *Arch Med Sci.* 2013;9(5):944–52.
15. Pedersen IB, Laurberg P, Knudsen N, Jørgensen T, Perrild H, Ovesen L, et al. Increase in incidence of hyperthyroidism predominantly occurs in young people after iodine fortification of salt in Denmark. *J Clin Endocrinol Metab.* 2006;91(10):3830–4.
16. Kahaly GJ, Dillmann WH. Thyroid hormone action in the heart. *Endocr Rev.* 2005;26(5):704–28.
17. Ozturk S, Dikbas O, Baltaci D, Ozyasar M, Erdem A, Ayhan SS, et al. Evaluation of atrial conduction abnormalities and left atrial mechanical functions in patients with subclinical thyroid disorders. *Endokrynol Pol.* 2012;63(4):286–93.
18. Gereben B, Zavacki AM, Ribich S, Kim BW, Huang SA, Simonides WS, et al. Cellular and molecular basis of deiodinase-regulated thyroid hormone signaling. *Endocr Rev.* 2008;29(7):898–938.
19. Biondi B, Palmieri EA, Lombardi G, Fazio S. Effects of thyroid hormone on cardiac function: The relative importance of heart rate, loading conditions, and myocardial contractility in the regulation of cardiac performance in human hyperthyroidism. *J Clin Endocrinol Metab.* 2002;87(3):968–74.
20. Danzi S, Klein I. Thyroid hormone and blood pressure regulation. *Curr Hypertens Rep.* 2003;5(6):513–20.
21. Cai Y, Ren Y, Shi J. Blood pressure levels in patients with subclinical thyroid dysfunction: A meta-analysis of cross-sectional data. *Hypertens Res [Internet].* 2011;34(10):1098–105. Available from: <http://dx.doi.org/10.1038/hr.2011.91>

22. Prisant LM, Gujral JS, Mulloy AL. Hyperthyroidism: a secondary cause of isolated systolic hypertension. *J Clin Hypertens (Greenwich)*. 2006;8(8):596–9.
23. Osman F, Franklyn JA, Holder RL, Sheppard MC, Gammie MD. Cardiovascular Manifestations of Hyperthyroidism Before and After Antithyroid Therapy. A Matched Case-Control Study. *J Am Coll Cardiol*. 2007;49(1):71–81.
24. Klein I, Danzi S. Thyroid disease and the heart. *Circulation*. 2007;116(15):1725–35.
25. Selmer C, Olesen JB, Hansen ML, Lindhardsen J, Olsen AMS, Madsen JC, et al. The spectrum of thyroid disease and risk of new onset atrial fibrillation: A large population cohort study. *BMJ*. 2012;345(7885):1–12.
26. Bruere H, Fauchier L, Brunet AB, Pierre B, Simeon E, Babuty D, et al. History of thyroid disorders in relation to clinical outcomes in Atrial fibrillation. *Am J Med* [Internet]. 2015;128(1):30–7. Available from: <http://dx.doi.org/10.1016/j.amjmed.2014.07.014>
27. Squizzato A, Gerdes VEA, Brandjes DPM, Büller HR, Stam J. Thyroid diseases and cerebrovascular disease. *Stroke*. 2005;36(10):2302–10.
28. Squizzato A, Romualdi E, Büller HR, Gerdes VEA. Clinical review: Thyroid dysfunction and effects on coagulation and fibrinolysis: A systematic review. *J Clin Endocrinol Metab*. 2007;92(7):2415–20.
29. Mirza SA. Association between increased mortality and mild thyroid dysfunction in cardiac patients. *South Med J*. 2008;101(3):221–2.
30. Allencherril J, Birnbaum I. Heart failure in thyrotoxic cardiomyopathy: Extracorporeal membrane oxygenation treatment for graves' disease. *J Extra Corpor Technol*. 2015;47(4):231–2.
31. Siu CW, Yeung CY, Lau CP, Kung AWC, Tse HF. Incidence, clinical characteristics and outcome of congestive heart failure as the initial presentation in patients with primary hyperthyroidism. *Heart*. 2007;93(4):483–7.
32. Yu YH, Bilezikian JP. Tachycardia-induced cardiomyopathy secondary to thyrotoxicosis: A young man with previously unrecognized Graves' disease. *Thyroid*. 2000;10(10):923–
33. Boccalandro C, Boccalandro F, Orlander P, Wei CF. Severe reversible dilated cardiomyopathy and hyperthyroidism: case report and review of the literature. *Endocr Pract*. 2003;9(2):140–6.
34. Ebisawa. irreversible cardiomyopathy due to thyrotoxicosis. 1375;
35. Hansen C, Fraiture B, Rouhi R, Otto E, Förster G, Kahaly G. HPLC glycosaminoglycan analysis in patients with Graves' disease. *Clin Sci*. 1997;92(5):511–7.
36. Kahaly GJ. The thyrocyte-fibrocyte link: Closing the loop in the pathogenesis of graves' disease? *J Clin Endocrinol Metab*. 2010;95(1):62–5.
37. Marvisi M, Zambrelli P, Brianti M, Civardi G, Lampugnani R, Delsignore R. Pulmonary hypertension is frequent in hyperthyroidism and normalizes after therapy. *Eur J Intern Med*. 2006;17(4):267–71.
38. Suki JH, Choi KI, Lee SH, Lee HG, Kim SM, Kim TI, et al. Prevalence of echocardiography criteria for the diagnosis of pulmonary hypertension in patients with Graves' disease: Before and after antithyroid treatment. *J Endocrinol Invest*. 2011;34(8 SUPPL.):229–34.
39. Chu JW, Kao PN, Faul JL, Doyle RL. High prevalence of autoimmune thyroid disease in pulmonary arterial hypertension. *Chest* [Internet]. 2002;122(5):1668–73. Available from: <http://dx.doi.org/10.1378/chest.122.5.1668>
40. Scicchitano P, Dentamaro I, Tunzi F, Ricci G, Carbonara S, Devito F, et al. Pulmonary hypertension in thyroid diseases. *Endocrine*. 2016;54(3):578–87.
41. Lozano HF, Sharma CN. Reversible pulmonary hypertension, tricuspid regurgitation and right-sided heart failure associated with hyperthyroidism: Case report and review of the literature. *Cardiol Rev*. 2004;12(6):299–305.
42. Lu M, Yang CB, Gao L, Zhao JJ. Mechanism of subclinical hypothyroidism accelerating endothelial dysfunction (Review). *Exp Ther Med*. 2015;9(1):3–10.
43. Marazuela M, Sanchez-Madrid F, Acevedo A, Larranaga E, De Landazuri MO. Expression of vascular adhesion molecules on human endothelia in autoimmune thyroid disorders. *Clin Exp Immunol*. 1995;102(2):328–34.

44. Kim EJ, Lyass A, Wang N, Massaro JM, Fox CS, Benjamin EJ, et al. Relation of hypothyroidism and incident atrial fibrillation (from the Framingham heart study). *Am Heart J* [Internet]. 2014;167(1):123–6. Available from: <http://dx.doi.org/10.1016/j.ahj.2013.10.012>
45. Bakiner O, Ertorer ME, Haydardedeoglu FE, Bozkirli E, Tutuncu NB, Demirag NG. Subclinical hypothyroidism is characterized by increased QT interval dispersion among women. *Med Princ Pract*. 2008;17(5):390–4.
46. Schenck JB, Rizvi AA, Lin T. Severe primary hypothyroidism manifesting with torsades de pointes. *Am J Med Sci*. 2006;331(3):154–6.
47. Schoenmakers N, De Graaff WE, Peters RHJ. Hypothyroidism as the cause of atrioventricular block in an elderly patient. *Netherlands Hear J*. 2008;16(2):57–9.
48. SuX, Peng H, Chen X, Wu X, Wang B. Hyperlipidemia and hypothyroidism. *Clin Chim Acta* [Internet]. 2022;527(September 2021):61–70. Available from: <https://doi.org/10.1016/j.cca.2022.01.006>
49. Montalvo D, Pérez-Treviño P, Madrazo-Aguirre K, González-Mondellini FA, Miranda-Roblero HO, Ramonfaur-Gracia D, et al. Underlying mechanism of the contractile dysfunction in atrophied ventricular myocytes from a murine model of hypothyroidism. *Cell Calcium* [Internet]. 2018;72(November 2017):26–38. Available from: <https://doi.org/10.1016/j.ceca.2018.01.005>
50. Biondi B, Palmieri EA, Lombardi G, Fazio S. Subclinical hypothyroidism and cardiac function. *Thyroid*. 2002;12(6):505–10.
51. Dattilo G, Crosca S, Tavella S, Marte F, Patanè S. Pericardial effusion associated with subclinical hypothyroidism. *Int J Cardiol* [Internet]. 2011;153(3):e47–50. Available from: <http://dx.doi.org/10.1016/j.ijcard.2009.03.090>
52. Schlüter KD, Piper HM. Cardiovascular actions of parathyroid hormone and parathyroid hormone-related peptide. *Cardiovasc Res*. 1998;37(1):34–41.
53. Andersson P, Rydberg E, Willenheimer R. Primary hyperparathyroidism and heart disease - A review. *Eur Heart J*. 2004;25(20):1776–87.
54. WANG E. PARATHYROID HORMONE SELECTIVELY INHIBITS L-TYPE CALCIUM CHANNELS IN SINGLE VASCULAR SMOOTH MUSCLE CELLS OF THE RAT BY. *Encycl Neurosci*. 2009;543–50.
55. Tastan I, Schreckenberg R, Mutti S, Abdallah Y, Piper HM, Schlüter KD. Parathyroid hormone improves contractile performance of adult rat ventricular cardiomyocytes at low concentrations in a non-acute way. *Cardiovasc Res*. 2009;82(1):77–83.
56. Zhang H, Gao Y, Wang Y, Yan Y, Yang Z, Miao D, et al. The effects of parathyroid hormone-related peptide on cardiac angiogenesis, apoptosis, and function in mice with myocardial infarction. *J Cell Biochem*. 2019;120(9):14745–55.
57. Schlüter KD, Weber M, Piper HM. Parathyroid hormone induces protein kinase C but not adenylate cyclase in adult cardiomyocytes and regulates cyclic AMP levels via protein kinase C-dependent phosphodiesterase activity. *Biochem J*. 1995;310(2):439–44.
58. Wang R, Wu L, Karpinski E, Pang PKT. The effects of parathyroid hormone on L-type voltage-dependent calcium channel currents in vascular smooth muscle cells and ventricular myocytes are mediated by a cyclic AMP dependent mechanism. *FEBS Lett*. 1991;282(2):331–4.
59. Rashid G, Bernheim J, Green J, Benchetrit S. Parathyroid hormone stimulates the endothelial nitric oxide synthase through protein kinase A and C pathways. *Nephrol Dial Transplant*. 2007;22(10):2831–7.
60. Shao JS, Cheng SL, Charlton-Kachigian N, Loewy AP, Towler DA. Teriparatide (Human Parathyroid Hormone (1-34)) Inhibits Osteogenic Vascular Calcification in Diabetic Low Density Lipoprotein Receptor-deficient Mice. *J Biol Chem* [Internet]. 2003;278(50):50195–202. Available from: <http://dx.doi.org/10.1074/jbc.M308825200>
61. Claudia Goetttsch. Parathyroid hormone - a critical bridge between bone metabolism and cardiovascular diseases. *Bone*. 2011;23(1):1–7.
62. Neves KR, Graciolli FG, Dos Reis LM, Graciolli RG, Neves CL, Magalhães AO, et al. Vascular calcification: Contribution of parathyroid hormone in renal failure. *Kidney Int*. 2007;71(12):1262–70.

63. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol.* 2004;15(8):2208–18.
64. Tomaschitz A, Ritz E, Pieske B, Rus-Machan J, Kienreich K, Verheyen N, et al. Aldosterone and parathyroid hormone interactions as mediators of metabolic and cardiovascular disease. *Metabolism [Internet].* 2014;63(1):20–31. Available from: <http://dx.doi.org/10.1016/j.metabol.2013.08.016>
65. Brown J, De Boer IH, Robinson-Cohen C, Siscovick DS, Kestenbaum B, Allison M, et al. Aldosterone, parathyroid hormone, and the use of renin-angiotensin-aldosterone system inhibitors: The multi-ethnic study of atherosclerosis. *J Clin Endocrinol Metab.* 2015;100(2):490–9.
66. Maniero C, Fassina A, Guzzardo V, Lenzini L, Amadori G, Pelizzo MR, et al. Primary hyperparathyroidism with concurrent primary aldosteronism. *Hypertension.* 2011;58(3):341–6.
67. Zheng MH, Li FXZ, Xu F, Lin X, Wang Y, Xu QS, et al. The Interplay Between the Renin-Angiotensin-Aldosterone System and Parathyroid Hormone. *Front Endocrinol (Lausanne).* 2020;11(August):1–12.
68. Taylor EN, Curhan GC, Forman JP. Parathyroid hormone and the risk of incident hypertension. *J Hypertens.* 2008;26(7):1390–4.
69. Yao L, Folsom AR, Pankow JS, Selvin E, Michos ED, Alonso A, et al. Parathyroid hormone and the risk of incident hypertension: The Atherosclerosis Risk in Communities study. *J Hypertens.* 2016;34(2):196–203.
70. Vlachakis ND, Frederics R, Velasquez M, Alexander N, Singer F, Maronde RF. Sympathetic System Function and Vascular Reactivity in Hypercalcemic Patients. *Hypertension.* 1982;4(3):452–8.
72. Saleh FN, Schirmer H, Sundsfjord J, Jorde R. Parathyroid hormone and left ventricular hypertrophy. *Eur Heart J.* 2003;24(22):2054–60.
73. Piovesan A, Molineri N, Casasso F, Emmolo I, Ugliengo G, Cesario F, et al. Left ventricular hypertrophy in primary hyperparathyroidism. Effects of successful parathyroidectomy. *Clin Endocrinol (Oxf).* 1999;50(3):321–8.
74. Bansal N, Zelnick L, Robinson-Cohen C, Hoofnagle AN, Ix JH, Lima JA, et al. Serum parathyroid hormone and 25-hydroxyvitamin d concentrations and risk of incident heart failure: The Multi-Ethnic Study of Atherosclerosis. *J Am Heart Assoc.* 2014;3(6):1–15.
75. Schierbeck LL, Jensen TS, Bang U, Jensen G, Køber L, Jensen JEB. Parathyroid hormone and vitamin D markers for cardiovascular and all cause mortality in heart failure. *Eur J Heart Fail.* 2011;13(6):626–32.
76. Witte KK, Byrom R, Gierula J, Paton MF, Jamil HA, Lowry JE, et al. Effects of Vitamin D on Cardiac Function in Patients With Chronic HF: The VINDICATE Study. *J Am Coll Cardiol [Internet].* 2016;67(22):2593–603. Available from: <http://dx.doi.org/10.1016/j.jacc.2016.03.508>
77. Iwata S, Walker MD, Di Tullio MR, Hyodo E, Jin Z, Liu R, et al. Aortic valve calcification in mild primary hyperparathyroidism. *J Clin Endocrinol Metab.* 2012;97(1):132–7.
78. Mihai R, Farndon JR. Parathyroid disease and calcium metabolism. *Br J Anaesth.* 2000;85(1):29–43.
79. Walker MD, Silverberg SJ. Cardiovascular aspects of primary hyperparathyroidism. *J Endocrinol Invest.* 2008;31(10):925–31.
80. JP Bilezikian, A Khan, JT Potts Jr M et al. *J Bone Miner Res. J Bone Min Res.* 2011;26(10):2317–37.
81. Çakırri L, Husi G, Minxuri D, Roko E, Vyshka G. Primary hypoparathyroidism presenting with heart failure and ventricular fibrillation. *Oxford Med Case Reports.* 2014;2014(4):77–9.
82. Bansal B, Bansal M, Bajpai P, Garewal HK. Hypocalcemic cardiomyopathy-different mechanisms in adult and pediatric cases. *J Clin Endocrinol Metab.* 2014;99(8):2627–32.
83. Kazmi AS, Wall BM. Reversible congestive heart failure related to profound hypocalcemia secondary to hypoparathyroidism. *Am J Med Sci [Internet].* 2007;333(4):226–9. Available from: <http://dx.doi.org/10.1097/MAJ.0b013e318039b9c6>